NEUROLOGICAL ASPECTS OF TROPICAL DISEASE

Cerebral malaria

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Abstract

Cerebral malaria may be the most common non-traumatic encephalopathy in the world. The pathogenesis is heterogenous and the neurological complications are often part of a multisystem dysfunction. The clinical presentation and pathophysiology differs between adults and children. Recent studies have elucidated the molecular mechanisms of pathogenesis and raised possible interventions. Antimalarial drugs, however, remain the only intervention that unequivocally affects outcome, although increasing resistance to the established antimalarial drugs is of grave concern. Artemisinin derivatives have made an impact on treatment, but other drugs may be required. With appropriate antimalarial drugs, the prognosis of cerebral malaria often depends on the management of other complications—for example, renal failure and acidosis. Neurological sequelae are increasingly recognised, but further research on the pathogenesis of coma and neurological damage is required to develop other ancillary treatments.

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Malaria is the most important of the parasitic diseases of humans, and its neurological complication, cerebral malaria is arguably one of the most common non-traumatic encephalopathies in the world. Malaria affects about 5% of the world's population at any time and causes somewhere between 0.5 and 2.5 million deaths each year. There are four species of human malaria, but *Plasmodium falciparum* causes nearly all the deaths and neurological complications. Severe malaria occurs predominantly in patients with little or no background immunity—that is, children growing up in endemic areas, or travellers or migrants who come from areas without malaria, but are exposed to malaria later in life. The manifestations of severe malaria differ depending on the age of the patient and previous exposure.[1] In the first 2 years of life severe anaemia is a common presenting feature of severe malaria. In older children seizures and cerebral malaria predominate; whereas in adults acute renal failure, acute pulmonary oedema, liver dysfunction, and cerebral malaria may all occur. Metabolic acidosis, mainly a lactic acidosis, is common at all ages. Severe malaria is a multisystem disease, and the outcome often depends on the degree of vital organ dysfunction.

P falciparum is transmitted by female Anopheles mosquitoes. In humans, although the parasite undergoes development in the liver, it is the erythrocytic cycle that is responsible for disease. The merozoites released by the liver invade the erythrocyte, and during a period of 48 hours, pass through morphologically distinct stages, before the meronts (schizonts) rupture the erythrocyte. Ring stages are seen in the peripheral blood, but trophozoites and meronts are usually absent, as they are sequestered within the deep vascular beds.

Pathological features of cerebral malaria

The histopathological hallmark of cerebral malaria is engorgement of cerebral capillaries and venules with parasitised red blood cells (PRBCs) and non-paratised RBCs (NPRBCs).[2] The brain is usually swollen at postmortem, although evidence of frank herniation is unusual in adults. The cut brain is slate grey, with petechial haemorrhages. The endothelium does not demonstrate microscopical damage,[2] but immunohistochemical staining suggests endothelial activation[3] and disruption of the blood-brain barrier.[4] Inflammatory cells and immune complex deposition are not consistent features in necropsy series to date[2 3] although some authors think that cerebral malaria has features of a diffuse encephalomyelitis.[5]

Sequestration

The sequestration of red cells containing mature forms of the parasite (trophozoites and meronts) in the microvasculature is thought to cause the major complications of falciparum malaria, particularly cerebral malaria.[6] This process varies considerably between organs (the brain is particularly affected) and at a microvascular level varies between vessels. The sequestration of PRBCs in the relatively hypoxic venous beds allows optimal parasite growth and prevents the PRBCs from being destroyed by the spleen.[7] It is the sequestered parasites that cause pathology in severe malaria, and prognosis is related to sequestered

biomass.[8 9] The peripheral blood parasite count is a relatively poor predictor of the size of this biomass. In a recent postmortem study of fatal falciparum malaria in adults, the median ratio of cerebral to peripheral blood parasitaemia was 40 (range 1.8–1500).[10] In this study, although most sequestered parasites were the mature stages not seen in the peripheral blood, there were considerably more ring stages than expected from a free mixing model. Patients who have died from non-neurological complications of falciparum malaria also show cerebral sequestration at necropsy, although the intensity is less in patients who die without preceding coma.[2] Many authors have commented on the lack of correlation between the necropsy findings and clinical features of cerebral malaria; although one study showed a correlation between the degree of PRBC sequestration and depth of coma on admission.[11] Some authors have suggested that cerebral malaria may occur in the absence of cerebral sequestration. These discrepancies can be explained by the variable interval between starting antimalarial treatment and death; fatal cases without cerebral sequestration have invariably received many days of antimalarial treatment before dying.

Cytoadherence

Sequestration is thought to be a specific interaction between PRBCs and the vascular endothelium (cytoadherence). This phenomenon seems to be mediated by plasmodium derived proteins on the surface of PRBCs and modified erythrocyte cell wall proteins and ligands on endothelial cells.The adhesion of the PRBCs reduces the microvascular blood flow,[12] which may explain organ and tissue dysfunction such as coma. The metabolically active sequestered parasites may compete with host tissues for substrates—for instance, glucose—and also produce toxins that interfere with host tissue metabolism. Unfortunately, there is no satisfactory animal model of human cerebral malaria. In vitro models show that cytoadherence begins when the parasites produce visible malaria pigment (usually becoming visible under light microscopy around 16 hours), which is maximal at the late stages.[7] Cytoadherence occurs predominately in capillaries and venules, as it is overcome by large shear stresses encountered on the arterial side.[13] Freshly isolated PRBCs capable of cytoadherence have electron dense "knobs" protruding from their surfaces, composed of proteins derived from the parasite, notably the adhesin *P falciparum* erythrocyte membrane protein-1 (PfEMP-1).[14] This family of large proteins (200–350 kDa) which are expressed on the exterior of PRBCs vary antigenically with time in cloned parasites. This programmed variation allows the parasites to evade host immune responses. These proteins have adhesive properties and are primarily responsible for cytoadherence. A family of more than 150 highly variable ("*var*") genes encode PfEMP-1, which can bind to several candidate endothelial receptors.[15] Some of these vascular receptors, such as the main candidate CD36, seem to be expressed at all times in a wide range of vascular beds and are regarded as constitutive; their expression is not related qualitatively or quantitatively to severity of disease.[16] Other receptors such as intracellular adhesion molecule-1 (ICAM-1) and endothelial selectin (E-selectin) are inducible,[17] with increased expression in the cerebral vessels of patients with cerebral malaria, which co-localises with sequestration, suggesting that they may be responsible for cytoadherence.[3 4] Monoclonal antibodies against ICAM-1 improve microcirculatory flow in ex vivo models of malaria sequestration,[12] but have not been evaluated in humans. The process of PRBC cytoadherence has several parallels to that of leucocyte adherence to the vascular endothelium. Firstly, rolling occurs along the endothelial surface, followed by static adherence, which reduces flow in packed partially obstructed vessels.

The clinical correlates of these in vitro models are poor. Parasitised red blood cells from Gambian children with cerebral malaria did not bind more avidly to C32 melanoma cells than isolates from children with less severe disease.[7 18] Although binding to CD36[19] has been shown to be directly proportional to parasitaemia, the degree of binding to CD36 cells correlated with biochemical indicators of disease severity in adult Thai with malaria,[19] rather than coma.[20] In adults with cerebral malaria there was an increase in vessels expressing ICAM-1 and E-selectin, but not other ligands[3]; whereas in Kenyan children, there was a relation between cerebral malaria and binding to CD36, ICAM-1[21] and a mutation in the ICAM-1,[22] although this was not confirmed in other sites in Africa.[23 24] Studies on peripheral blood parasites reflect the entire repertoire of adhesins, and may not be representative of cytoadherence in a particular organ.

Rosetting and agglutination

The adherence of NPRBCs to PRBCs (rosetting) and PRBCs to PRBCs (agglutination), have also been implicated in the pathogenesis of cerebral malaria, although most clinical studies have failed to show an association. In rosetting, the *var* genes seem to be responsible for the ligands[25] and this intererythrocytic interaction is pH and heparin sensitive.[26] It can be disrupted by antibodies to *P falciparum*,[18] glycosaminoglycans, sulfated glycoconjugates in a strain and isolate specific manner.[27] Rosettes are disrupted at high flow rates, although they reform at lower shear stresses, aggravating the venular obstruction in a rodent ex vivo model of sequestration.[28] Increased rosette formation was found in Gambian children with cerebral malaria, with a corresponding lack of antirosetting antibodies,[18] whereas studies from other parts of the world did not show such an association.[24 29] The contribution of agglutination to the pathophysiology of severe malaria is unclear.

Red cell deformability

As the parasite grows within the RBCs, the erythrocyte becomes less deformable,[30] which

may contribute to the RBC destruction and impair the microcirculatory flow. The reduction in red cell deformability not only occurs in PRBCs, but also the NPRBCs. The NPRBCs have to undergo considerable deformation as they squeeze through the sequestered microcirculation. Microvascular perfusion in severe falciparum malaria is therefore limited by mechanical obstruction, adherence of other RBCs, and the stiffness of the non-adherent RBCs. Red cell deformity measured at low shear rates encountered in capillaries and venules, proved the most powerful prognostic indicator of severe malaria in a study of Thai adults,[31] although not associated with the syndrome of cerebral malaria itself. Similar studies in Kenyan children also showed a strong association with severe disease and a predictable increase in red cell deformity with blood transfusions.[32]

CYTOKINES

Blood concentrations of proinflammatory cytokines are raised in cerebral malaria,[33 34] as in many severe infections. Tumour necrosis factor-α (TNF-α) upregulates endothelial cytoadherence receptors and can cause hypoglycaemia and dyserythropoiesis, which are features of severe disease.

In African children, high concentrations of TNF-α are associated with coma, hypoglycaemia, hyperparasitaemia, and death.[33 34] Early studies suggested that increases in proinflammatory cytokine concentrations were associated with cerebral malaria, generating the hypotheses that cytokines produced coma. Thus Clarke *et al* suggest that TNF-α induces the release of nitric oxide (NO), which interferes with synaptic transmission, causing coma.[35] More recent studies in adults indicate that the increases in cytokine concentration relate more to overall severity. Plasma concentrations of TNF-α, interleukin (IL)-6, and IL-10 were higher in Vietnamese adults who died with severe malaria than survivors; but these increases were not associated with cerebral malaria.[36] Indeed, concentrations of proinflammatory cytokines were significantly lower in patients with pure cerebral malaria than in those with multiple organ dysfunction. Fatal malaria is associated with a relative deficiency of IL-10 production, an anti-inflammatory cytokine that controls the production of the proinflammatory cytokines. Persuasive evidence for a role of proinflammatory cytokines in lethal malaria comes from the finding that Gambian children homozygous for the 308 TNF promoter polymorphism allele are at a significantly increased risk of dying of cerebral malaria.[37 38]

However, there are inconsistencies. In patients with severe malaria, the blood concentrations of TNF-α receptors are markedly increased and bioactive TNF-α is seldom detectable.[39] There is considerable overlap between the distribution of cytokine concentrations in the different clinical patterns of malaria.[34] Concentrations of TNF-α measured in paroxysms of uncomplicated *P vivax* infections are as high as those measured in patients with cerebral malaria,[40] but this infection rarely causes neurological disturbances. The administration of monoclonal anti-TNF, reduced temperature, indicating bioactivity against pyrogenic cytokines,[41] but did not effect outcome.[42] Plasma concentrations of nitrate and nitrite (so called reactive nitrogen intermediates (RNI)), surrogate measures for NO, have been shown to be raised in some series but low in others.[43 44] The RNIs are crude measures of NO production, as they are also influenced markedly by diet, and their elimination is via the kidney. In Papua New Guinea, these metabolites were highest in children with cerebral malaria, particularly those who died.[45] In African children, NO production was lowest in those aged 1–5 years, the age at which children are most susceptible to cerebral malaria.[46] The metabolites are lower in plasma of children admitted with cerebral malaria,[47] but higher in the CSF of children who died in one study,[48] but not in another.[49] In Vietnamese and Thai adults the increase in plasma concentration of RNI in severe malaria (particularly fatal cases) was accounted for entirely by renal impairment, and thus reduced RNI clearance rather than cerebral involvement.[50] Therefore, if cytokines and NO have an important pathogenic role, it is likely to be at the local tissue level, rather than systemically.

DEFINITION OF CEREBRAL MALARIA

The term "cerebral malaria" has often been used loosely in the medical literature to describe any disturbance of the CNS in a malaria infection. In the case reports of the cerebral involvement caused by *P vivax*, other causes of an encephalopathy or mixed infections with *P falciparum* have not been adequately excluded. In falciparum malaria, disturbances of consciousness can be caused by systemic complications—for example, fever, hypoglycaemia, hyponatraemia, and uraemia. To allow comparison between patient populations in different countries, a strict definition of cerebral malaria was suggested[51 52]: defined as a deep level of unconsciousness (inability to localise a painful stimulus) in the presence of a *P falciparum* asexual parasitaemia, after the correction of hypoglycaemia and exclusion of other encephalopathies, especially bacterial meningitis and locally prevalent viral encephalitides. In adults, coma was required for more than 6 hours after a generalised convulsion to exclude a transient postictal state (which rarely lasts more than 1 hour), although in children this was reduced to 1 hour.[53] In fatal cases, the diagnosis of cerebral malaria is supported by finding cerebral capillaries and venules packed with PRBCs. These features may be absent if the patient dies after several days of treatment, and are not specific for cerebral malaria. In clinical practice, any impairment of consciousness or other sign of cerebral dysfunction is an indication for parenteral treatment and intensive care management.

Cerebral malaria in adults

CLINICAL FEATURES

Cerebral malaria is a diffuse encephalopathy in which focal neurological signs are relatively unusual. The patient is febrile and unconscious with divergent gaze and variable tone.[54] There may be passive resistance to neck flexion, but of a lesser degree to the "meningism" associated with meningitis. There is no rash, and no lymphadenopathy. As cerebral malaria is often accompanied by multisystem dysfunction, an assessment of the degree of anaemia, jaundice and, most importantly, the presence of acidotic (Kussmaul's) breathing is important. The prognosis of cerebral malaria worsens considerably with coexistent renal failure, severe jaundice, or metabolic acidosis. The metabolic acidosis is caused by either an acute renal failure, or a lactic acidosis, or a combination of both. Acute pulmonary oedema may occur. Rarely, patients with severe malaria have disseminated intravascular coagulation[52] and evidence of bleeding, usually from the upper gastrointestinal tract but sometimes in the skin. The pulse is usually rapid and full, with a low or normal blood pressure. The peripheries are well perfused, although shock may occur and is often terminal. Hypoglycaemia (plasma glucose<2.2 mmol/l) is common in severe malaria, occurring in about 8% of adults[55] and about 20% of children with cerebral malaria.[1 56] It is usually not accompanied by noticeable sweating or gooseflesh or other physical signs of hypoglycaemia. All patients with severe malaria should have frequent checks of blood glucose. Restoration of normoglycaemia, however, is often not associated with a change in the level of consciousness.

On direct ophthalmoscopy retinal haemorrhages are found in about 15% of patients.[57] These are boat or flame shaped and sometimes resemble Roth spots with a pale centre. They usually spare the maculae. Indirect ophthalmoscopy discloses haemorrhages in a much higher proportion of patients.[58] These haemorrhages seldom involve the macula. Areas of unusual retinal "whitening" may also be seen and occasional cotton wool spots.[58] Papilloedema is very unusual in adults. The pupillary reactions are usually normal and the range of eye movements full, although gaze is dysconjugate. Sixth nerve palsies may occur rarely.[54] The corneal reflexes are usually present although in very deep coma they may be lost. The remainder of the cranial nerve examination is usually normal. A pout reflex may sometimes be elicited and bruxism is common but other "frontal release" signs are unusual.[54] Stereotyped movements, commonly seen in encephalitides, are not seen in cerebral malaria. Tone and reflexes are variable. The abdominal reflexes are almost always absent, the plantars often upgoing, and ankle and patellar clonus can sometimes be elicited in hypertonic patients.[54]

SEIZURES

The incidence of convulsions in adults with cerebral malaria varies. In the early 1980s studies conducted in Thailand and Vietnam, 50% of adults with cerebral malaria had generalised seizures,[59] whereas in these countries in the 1990s the incidence was less than 10%. The reason for this difference is not clear. Possible explanations include differences in parasite virulence characteristics, or possibly the decrease in the use of chloroquine pretreatment. Partial motor seizures may also occur and in occasional cases the evidence for seizure activity is subtle, such as repetitive eye or hand movements, and may be easily overlooked. Subtle evidence for seizure activity seems to be more common in children than in adults. The level of consciousness after a seizure is usually lower than that preceding it. Status epilepticus is unusual in adults, although more than one seizure is common.[59]

OUTCOME

The overall mortality of adult cerebral malaria is about 20%.[52] Mortality depends on the associated vital organ dysfunction. In patients with "pure" cerebral malaria and no other evidence of vital organ dysfunction the mortality is 8%, whereas it rises towards 50% with associated acute renal failure and metabolic acidosis. Mortality is also dependent on the availability of intensive care facilities. If the patient can be ventilated if needed and renal replacement therapy (preferably haemofiltration) provided, and there is careful nursing of the unconscious patient, then mortality is reduced.The patient may die from a sudden acute respiratory arrest, often after a period of respiratory irregularity, but with a normal blood pressure. Other patients may die from shock and others from hypoxia and hypotension secondary to acute pulmonary oedema or sometimes aspiration pneumonia. Most deaths occur within 48 hours of admission. Full recovery of consciousness takes a median of 2 days in patients with a summated Glasgow coma score <11 but occasional adult patients may take more than 1 week to recover consciousness.

Cerebral malaria in African children

In African children growing up in malarious endemic areas, severe falciparum malaria usually manifests as seizures, impaired consciousness, or metabolic acidosis presenting as respiratory distress or severe anaemia.[60] Compared with adults, children have a higher incidence of seizures[61]; the incidence and pattern of neurological sequelae are different and they often die with features of brain death.[1] African children rarely develop renal failure or pulmonary oedema.

In older children, cerebral malaria can be defined as in adults. The Blantyre coma scale (table 1), was devised to assess young children with severe malaria[53] and a summated score$\leqslant$2 is used to define cerebral malaria in many studies.[34 62] The Blantyre coma scale has similar components to the Glasgow coma scale, but measures different responses. However, there is considerable disagreement between observers in assessing the scale,[63] and the scale does not address the inability of young infants to localise a painful stimulus.[63]

Table 1 Blantyre coma scale[53]

Verbal	0: No cry
	1: Inappropriate cry or moan
	2: Appropriate cry
Motor	0: Non-specific or no response
	1: Withdrawal from pain
	2: Localises pain
Eye	0: Not directed
	1: Directed eye movements

African children with cerebral malaria are older (40–45 months of age), than children with other complications of the disease,[60] but cerebral malaria is rarely encountered after the age of 10 years in people exposed to *P falciparum* since birth. Cerebral malaria presents usually with a 1–4 day history of fever and convulsions, the second often precipitates coma.[53 62] Focal motor and generalised tonic-clonic convulsions are the most common clinically detected seizures,[64 65] but subtle or subclinical seizures detected with EEG are also common.[66] Furthermore in some children, the level of consciousness improves with the administration of anticonvulsant drugs, suggesting that seizures contribute to the coma. Seizures are associated with a poor outcome,[53 67] particularly prolonged seizures.[64] Between seizures the EEG shows bilateral diffuse slowing of the brain waves, often asymmetric (not inevitably associated with clinical signs).[65]

Most African children with cerebral malaria survive with appropriate treatment, regaining consciousness within 48–72 hours of starting treatment.[53 62 68 69] The median time for recovery of consciousness is 32.3 hours (95% CI 23.4–41.1). In children, a median of 10.9% (95% CI 8.3–13.5) have neurological sequelae, a median 18.69% (95% CI 16.3–21.0) die.[1] Most deaths occur within 24 hours of starting treatment,[53 60 68 70] usually with brainstem signs, respiratory arrest, or overwhelming acidosis.

BRAIN SWELLING

Opening CSF pressures are raised in most African children with cerebral malaria[70 71] and there is evidence of brain swelling on CT[72] and at postmortem.[68] Kenyan children dying with cerebral malaria had clinical signs compatible with transtentorial herniation,[70] and half of the children had sonographic features of progressive intracranial hypertension during the agonal phases.[73] In a postmortem study of seven Nigerian children dying of cerebral malaria, transtentorial herniation was seen in one, and three others had evidence of brain oedema.[68] Monitoring intracranial pressure (ICP) confirmed that children deeply unconscious from cerebral malaria had raised ICP[74] and those children who developed severe intracranial hypertension either died or survived with severe neurological sequelae.

The most likely cause of raised ICP in cerebral malaria is an increase in cerebral blood volume,[70] particularly during the initial stages and in those children with moderate degrees of intracranial hypertension. Cerebral blood volume could be increased by the sequestration of PRBCs in the vascular compartment, either acting as a diffuse space occupying lesion or obstructing venous outflow.[70] An increased cerebral blood flow[72 75] could be caused by other features of cerebral malaria, such as seizures, hyperthermia, and anaemia. Kenyan children with severe neurological sequelae have tomographic evidence of cytotoxic oedema during recovery that may contribute to the severe intracranial hypertension.[72]

Whether intracranial hypertension is a primary pathophysiological process remains to be established. Mannitol was effective in lowering the ICP and may have prevented children with mild degrees of intracranial hypertension from dying or developing neurological sequelae, but it did not prevent the development of intractable intracranial hypertension in those children with a poor outcome.[74]

NEUROLOGICAL SEQUELAE

Neurological sequelae are associated with protracted seizures,[64 67] prolonged and deep coma,[64 67] hypoglycaemia,[64 67] and severe anaemia in some studies,[67] but not in others.[64] Some neurological deficits are transient (for example, ataxia), whereas others (for example, hemiparesis and cortical blindness), often improve over months, although they may not completely resolve. African children with severe neurological sequelae (spastic tetraparesis, vegetative states) usually die within a few months of discharge. More subtle deficits—for example, cognitive difficulties, and language and behavioural problems—are increasingly recognised. A study of 87 children with impaired consciousness found impairment of executive functions in children without obvious neurological deficits.[76] The incidence of epilepsy after cerebral malaria is not determined, although often reported.[1] Furthermore, as the seizures that occur during the acute illness are often focal, repetitive, or prolonged, damage to the hippocampus may occur, producing memory impairment and complex partial seizures, which may be underreported.

The causes of the sequelae are largely unknown and are likely to be multifactorial. Severe neurological sequelae are associated with severe intracranial hypertension.[74] Half of the children with hemiparesis have stenosis or occlusion of the basal cerebral arteries demonstrated by angiography[77 78] or transcranial Doppler.[73] The cause of large vessel disease is unknown but may be related to vasospasm or underlying conditions such as haemoglobinopathies. Some children with hemiparesis have the CT appearances of hemiconvulsion-hemiparesis syndrome. Blindness is usually cortical,[1] often follows seizures, and is usually associated by evidence of more diffuse damage, although it can occur in isolation. Brain damage could be caused by a mismatch between the delivery of oxygen (anaemia, decreased microcirculatory flow) and glucose (hypoglycaemia), in the presence of increased demand (seizures, fever). The generation of excitotoxins (seizures, hypoglycaemia),[49] reactive oxygen species (during reperfusion of the microcirculatory bed) or toxins produced by the parasite may also contribute.[1]

Table 2 Antimalarial treatment of cerebral malaria

	*Loading**	*Maintenance*
Cinchona alkaloid:		
Quinine dihydrochloride		
Intravenous	7 mg salt/kg over 30 min (infusion pump) followed immediately by 10 mg/kg over 4 h[101]	10 mg/kg over 4h repeated every 8–12 h‡§ [101,102]
	20 mg salt/kg over 4 h[102]	Same as above
Intramuscular	20 mg salt/kg (dilute iv formulation to 60 mg/ml given by deep im injection divided between both anterior thighs)[101102]	10 mg salt/kg repeated every 8–12 h‡¶ [101102]
Quinidine gluconate		
Intravenous	10 mg salt/kg¶ infused over 1–2 h[95] or 20 mg salt/kg infused over 4 h[103]	0.02 mg salt/kg/min continuously for up to 72 h†‡§ [95] 10 mg salt/kg infused over 4 h every 8–12 h†§ [103]
Artemisinin derivatives:**		
Artesunate††		
Intravenous	3.2 mg/kg	1.6 mg/kg repeated 12–24 hourly‡‡
Artemether		
Intramuscular	3.2 mg/kg[104]	1.6 mg/kg repeated 12–24 hourly‡‡

*Avoid loading dose if quinine, quinidine, or mefloquine taken in previous 24 h.
†Adjust rate of quinidine infusion to maintain blood concentration at 3–7 mg/l and prevent prolongation of ECG QRS>50%, QTc>25% of pretreatment values.
‡Change to oral quinine as soon as possible and complete 7 days of treatment.
§Add 1 g/day tetracycline in four divided doses for 7 days in non-pregnant adults in some areas.
¶This dose may be too low.
**Not marketed/licensed in many countries.
††Artesunate is reconstituted with bicarbonate solution immediately before use.
‡‡Change to oral mefloquine (single dose 15–25 mg/kg; max 1500 mg) as soon as possible.

Seizures and malaria

Seizures are the other common neurological manifestation of falciparum malaria, often precipitating admission to hospital. *P falciparum* seems to be particularly epileptogenic because it was the most common cause of seizures in children admitted to a Kenyan hospital[61] and more often associated with seizures compared with *P vivax* infections in Thai children.[79] Although fever may precipitate some seizures, most seizures occur when the rectal temperatures are less than 38.0°C.[61] By comparison with simple febrile seizures, the seizures in malaria are often recurrent, and 84% of the seizures are complex, most often with a focal nature.[61] The seizures may be caused by intracranial sequestration of metabolically active parasites or "toxins" produced by the parasites, but seem not to be associated with hypoglycaemia and hyponatraemia.[53 61] Some antimalarial drugs—for example, chloroquinine—may precipitate seizures.[80]

Management of patients with suspected cerebral malaria

Cerebral malaria is a medical emergency demanding urgent clinical assessment and treatment. Impairment of consciousness, convulsions, and other neurological features should raise the possibility of cerebral malaria in any person who might possibly have been exposed to this infection during the previous year. Most cases occur within 3 months of exposure. Such cases deserve transfer to the highest available level of care; where an appropriate antimalarial drug should be administered as soon as possible, ideally by the parenteral route. Complications of cerebral malaria, such as convulsions, hypoglycaemia, and hyperpyrexia, should be prevented or detected and treated early. Fluid, electrolyte, and acid-base balance may need correction. Skilled nursing care of the unconscious patient is crucial. Ancillary treatments should be avoided unless they have proved safe and effective.

The management of cerebral malaria is similar to that of any seriously ill unconscious patient. Intensive care with rehydration and thereafter careful fluid balance management are necessary to navigate the narrow divide between underhydration and worsening renal impairment and lactic acidosis, and overhydration and pulmonary oedema. Children are less likely to develop pulmonary oedema and more likely than adults to be hypovolaemic and underperfused. Many require rapid restoration of an adequate circulating blood volume.[81] Adults with severe malaria are particularly likely to develop the adult respiratory distress syndrome, more so than patients with bacterial septicaemia, so management is aided considerably by monitoring of central venous pressure, and if necessary, pulmonary artery occlusion pressure. Blood transfusion is indicated when the packed cell volume falls below 20%, and may be beneficial above this threshold. The blood glucose must be checked often and hypoglycaemia must be corrected. The stomach should be drained via a nasogastric tube. If ventilation is required, an experienced operator should perform intubation. Hypoxia and hypocapnoea may cause a fatal rise in ICP.[82] A lumbar puncture should be performed to exclude meningitis. In patients with acute renal failure or severe acidosis, haemofiltration should be started early if available.

Specific parenteral antimalarial treatment is the only intervention that unequivocally affects the outcome of cerebral malaria. Resistance has meant that chloroquine can no longer be relied on in most tropical countries. The Cinchona alkaloid quinine (or in the United States its diastereomer quinidine) remains the mainstay of antimalarial treatment of severe malaria (table 2). There has been controversy over many years over the optimum dosage and methods of administering quinine in severe malaria. Quinine must be given with an adequate loading dose (20 mg/kg of the dihydrochloride salt infused over 4 hours) to ensure that parasiticidal concentrations are reached in blood as soon as possible in the dis-

ease. In Zambian children a loading dose was associated with a shorter duration of coma and faster parasite clearance and resolution of fever.[83] Thereafter 30 mg/kg/day is given for 7 days, usually in 2–4 hour infusions of 10 mg/kg every 8 hours. Infusion rates must be monitored and these drugs must not be given by manual intravenous injection. The dose of quinine is reduced by 30–50% after 48 hours if there is no evidence of clinical improvement.[84] Oral treatment should be substituted when the patient can swallow reliably. Quinine is a powerful stimulant of pancreatic insulin secretion and may cause iatrogenic hypoglycaemia,[55] particularly in pregnant women.

Artemisinin (qinghaosu) derivatives of the plant *Artemisia annua* have been used extensively in the treatment of cerebral and other forms of severe falciparum malaria.[85 86] In uncomplicated malaria, these compounds clear parasitaemia and fever faster than the cinchona alkaloids, but although in recent large randomised controlled trials of intramuscular artemether and quinine in African children,[87] and Vietnamese adults,[88] there was no improvement in the mortality. These trials had only limited power to detect mortality reductions; none were powered to detect a reduction of <30%. A meta-analysis of these and other randomised trials indicates that in adults artemether did reduce mortality (by about one fifth), but there was no convincing difference in children.[89] Nevertheless, because of their safety and simplicity in administration, and declining sensitivity to quinine in some areas, they may well supercede quinine as the treatment of choice for severe malaria. Suppository formulations of artemisinin and artesunate have proved effective in cerebral and severe falciparum malaria.[90] Although concerns about neurotoxicity have arisen from animal studies, no significant side effects have been documented in humans and there is not an increased incidence of neurological sequelae.[89] In many parts of the world, complete cure requires the addition of a course of oral sulfadoxine/pyrimethamine or tetracycline/doxycycline for 7 days (clindamycin in pregnant women and children), which is started as soon as the patient is able to swallow tablets.

Hypovolaemia must be excluded in acidotic patients. Renal replacement, preferably using haemofiltration, should be started early in patients with acute hypercatabolic renal failure. Patients developing pulmonary oedema should be ventilated and overhydration excluded. Patients who deteriorate suddenly should be treated with glucose (if hypoglycaemia cannot be excluded rapidly) and broad spectrum antibiotics as concomitant septicaemia is not uncommon.

ANCILLARY TREATMENTS

Phenobarbital (3.5 mg intramuscularly) reduced the frequency of convulsions in adults,[59] but higher doses are needed to prevent convulsions in children.[91] In a recent double blind controlled trial in Kenyan children, phenobarbital (20 mg/kg) reduced seizures by 50%, but doubled the mortality.[92] There seemed to be an interaction with diazepam in these unventilated children. There was not a reduction in long term neurological sequelae.[92] Brain swelling should be excluded by imaging in patients who show a deteriorating level of consciousness and appearance of neurological abnormalities in the absence of hypoglycaemia. If there is evidence of cerebral swelling, 20% mannitol solution should be infused.[74] In adults, corticosteroids did not benefit patients with CM[51 93]; consciousness was prolonged, and there was an increased incidence of infection and gastrointestinal bleeding in the corticosteroid treated group.[51]

The use of exchange transfusion has been reported in more than 100 published cases of severe falciparum malaria, but no adequate randomised control data are available.[86 94 95] On empirical grounds, this intervention is probably justified when peripheral parasitaemia exceeds 10% of circulating erythrocytes in a presumed non-immune patient who has deteriorated on optimal conventional treatment.

Management of cerebral malaria in children is similar to adults. Dehydration and hypoglycaemia are more common in children and should be treated aggressively. Hypoglycaemia is often recurrent. The timing of the lumbar puncture to exclude other CNS infections is controversial.[74 96] The disposition of antimalarial drugs may be different in children.[97] Blood transfusions may be needed to correct severe anaemia and acidosis, and exchange transfusions for hyperparasitaemia have been used in American children.[98] The role of ancillary therapies is controversial. Desferrioxamine has not been shown to be of any benefit in adults or African children; indeed mortality was increased in desferrioxamine recipients in a more recent trial.[99] Pentoxifylline seems to shorten the duration of coma in African children,[100] but the trial was too small to detect differences in mortality.

Conclusion

Cerebral malaria is common and should be considered in any patient with impairment of consciousness. Urgent treatment with appropriate antimalarial drugs is required, but the prognosis often depends on the management of other complications—for example, renal failure, acidosis. Therapies that interfere with underlying pathophysiological processes—for example, reduced red cell deformability and cytoadherence—require further investigation. Further research on the pathogenesis of coma and neurological damage is required to develop other ancillary treatments.

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1 Newton CR, Krishna S. Severe falciparum malaria in children: current understanding of pathophysiology and supportive treatment. *Pharmacol Ther* 1998;**79**:1–53.
2 MacPherson GG, Warrell MJ, White NJ, *et al*. Human cerebral malaria. A quantitative ultrastructural analysis of parasitized erythrocyte sequestration. *Am J Pathol* 1985; **119**:385–401.
3 Turner GDH, Morrison H, Jones M, *et al*. An immunohistiochemical study of the pathology of fatal malaria. *Am J Pathol* 1994;**145**:1057–69.

4 Brown H, Hien TT, Day N, *et al*. Evidence of blood-brain barrier dysfunction in human cerebral malaria. *Neuropathol Appl Neurobiol* 1999;**25**:331–40.
5 Toro G, Roman G. Cerebral malaria. A disseminated vasculomyelinopathy. *Arch Neurol* 1978;**35**:271–5.
6 White NJ, Ho M. The pathophysiology of malaria. *Adv Parasitol* 1992;**31**:83–173.
7 Marsh K, Marsh VM, Brown J, *et al*. Plasmodium falciparum: the behavior of clinical isolates in an in vitro model of infected red blood cell sequestration. *Exp Parasitol* 1988;**65**:202–8.
8 Davis TME, Krishna S, Looareesuwan S, *et al*. Erythrocyte sequestration and anemia in severe falciparum malaria. *J Clin Invest* 1990;**86**:793–800.
9 Silamut K, White NJ. Relation of the stage of parasite development in the peripheral blood to prognosis in severe falciparum malaria. *Trans R Soc Trop Med Hyg* 1993;**87**:436–43.
10 Silamut K, Phu NH, Whitty C, *et al*. A quantitative analysis of the microvascular sequestration of malaria parasites in the human brain. *Am J Pathol* 1999;**155**:395–410.
11 Riganti M, Pongponratn E, Tegoshi T, *et al*. Human cerebral malaria in Thailand: a clinico-pathological correlation. *Immunol Lett* 1990;**25**:199–205.
12 Kaul DK, Liu XD, Nagel RL, *et al*. Microvascular hemodynamics and in vivo evidence for the role of intercellular adhesion molecule-1 in the sequestration of infected red blood cells in a mouse model of lethal malaria. *Am J Trop Med Hyg* 1998;**58**:240–7.
13 Nash GB, Cooke BM, Marsh K, *et al*. Rheological analysis of the adhesive interactions of red blood cells parasitized by Plasmodium falciparum. *Blood* 1992;**79**:798–807.
14 Fujioka H, Aikawa M. The molecular basis of pathogenesis of cerebral malaria. *Microb Pathog* 1996;**20**:63–72.
15 Borst P, Bitter W, McCulloch R, *et al*. Antigenic variation in malaria: minireview. *Cell* 1995;**82**:1–4.
16 Berendt AR, Ferguson DJ, Gardner J, *et al*. Molecular mechanisms of sequestration in malaria. *Parasitology* 1994; **108**(suppl):S19–28.
17 Berendt AR, Simmons DL, Tansey J, *et al*. Intracellular adhesion molecule-1 is an endothelial cell adhesion receptor for Plasmodium falciparum. *Nature* 1989;**341**:57–9.
18 Treutiger CJ, Hedlund I, Helmby H, *et al*. Rosette formation in Plasmodium falciparum isolates and anti-rosette activity of sera from Gambians with cerebral or uncomplicated malaria. *Am J Trop Med Hyg* 1992;**46**:503–10.
19 Ockenhouse CF, Ho M, Tandon NN, *et al*. Molecular basis of sequestration in severe and uncomplicated Plasmodium falciparum malaria: differential adhesion of infected erythrocytes to CD36 and ICAM-1. *J Infect Dis* 1991;**164**:163–9.
20 Ho M, Singh B, Looareesuwan S, *et al*. Clinical correlates of in vitro Plasmodium falciparum cytoadherence. *Infect Immun* 1991;**59**:873–8.
21 Newbold C, Warn P, Black G, *et al*. Receptor-specific adhesion and clinical disease in Plasmodium falciparum. *Am J Trop Med Hyg* 1997;**57**:389–98.
22 Fernandez RD, Craig AG, Kyes SA, *et al*. A high frequency African coding polymorphism in the N-terminal domain of ICAM-1 predisposing to cerebral malaria in Kenya. *Hum Mol Genet* 1997;**6**:1357–60.
23 Bellamy R, Kwiatkowski D, Hill AV. Absence of an association between intercellular adhesion molecule 1, complement receptor 1 and interleukin 1 receptor antagonist gene polymorphisms and severe malaria in a West African population. *Trans R Soc Trop Med Hyg* 1998;**92**:312–16.
24 Rogerson SJ, Tembenu R, Dobano C, *et al*. Cytoadherence characteristics of Plasmodium falciparum-infected erythrocytes from Malawian children with severe and uncomplicated malaria. *Am J Trop Med Hyg* 1999;**61**:467–72.
25 Rowe A, Newbold CI, Marsh K. Plasmodium falciparum rosetting is associated with malaria severity in Kenya. *Nature* 1997;**63**:2323–6.
26 Carlson J, Helmby H, Hill AV, *et al*. Human cerebral malaria: association with erythrocyte rosetting and lack of anti-rosetting antibodies. *Lancet* 1990;**336**:1457–60.
27 Barragan A, Spillmann D, Kremsner PG, *et al*. Plasmodium falciparum: molecular background to strain-specific rosette disruption by glycosaminoglycans and sulfated glycoconjugates. *Exp Parasitol* 1999;**91**:133–43.
28 Kaul DK, Roth EF, Nagel RL, *et al*. Rosetting of Plasmodium falciparum-infected red blood cells with uninfected red blood cells enhances microvascular obstruction under flow conditions. *Blood* 1991;**78**:812–19.
29 Rowe A, Obeiro J, Newbold CI, *et al*. Plasmodium falciparum rosetting is associated with malaria severity in Kenya. *Infect Immun* 1995;**63**:2323–6.
30 Cranston HA, Boylan CW, Carroll GL, *et al*. Plasmodium falciparum maturation abolishes physiologic red cell deformability. *Science* 1984;**223**:400–3.
31 Dondorp AM, Angus BJ, Hardeman MR, *et al*. Prognostic significance of reduced red blood cell deformability in severe falciparum malaria. *Am J Trop Med Hyg* 1997;**57**: 507–11.
32 Dondorp AM, Nyanoti M, Mithwani S, *et al*. Reduced red cell deformability in the pathogenesis of severe falciparum malaria and its restoration by blood transfusion. *Am J Trop Med Hyg* 2000;(in press).
33 Grau GE, Taylor TE, Molyneux ME, *et al*. Tumor necrosis factor and disease severity in children with falciparum malaria. *N Engl J Med* 1989;**320**:1586–91.
34 Kwiatkowski D, Hill AV, Sambou I, *et al*. TNF concentration in fatal cerebral, non-fatal cerebral, and uncomplicated Plasmodium falciparum malaria. *Lancet* 1990;**336**:1201–4.
35 Clark IA, Rockett KA, Cowden WB. Possible central role of nitric oxide in conditions clinically similar to cerebral malaria. *Lancet* 1992;**340**:894–6.
36 Day NP, Hien TT, Schollaardt T, *et al*. The prognostic and pathophysiologic role of pro- and antiinflammatory cytokines in severe malaria. *J Infect Dis* 1999;**180**:1288–97.
37 McGuire W, Hill AVS, Allsopp CEM, *et al*. Variation in the TNF-α promoter region associated with the susceptibility to cerebral malaria. *Nature* 1994;**371**:508–10.
38 McGuire W, Knight JC, Hill AV, *et al*. Severe malarial anemia and cerebral malaria are associated with different tumor necrosis factor promoter alleles. *J Infect Dis* 1999;**179**:287–90.
39 Kern P, Hemmer CJ, Gallati H, *et al*. Soluble tumor necrosis factor receptors correlate with parasitemia and disease severity in human malaria. *J Infect Dis* 1992;**166**:930–4.
40 Karunaweera ND, Grau GE, Gamage P, *et al*. Dynamics of fever and serum TNF levels are closely associated during clinical paroxysms in Plasmodium vivax malaria. *Proc Natl Acad Sci USA* 1992;**89**:3200–3.
41 Kwiatkowski D, Molyneux ME, Stephens S, *et al*. Anti-TNF therapy inhibits fever in cerebral malaria. *Q J Med* 1993;**86**:91–8.
42 van Hensbroek MB, Palmer A, Onyiorah E, *et al*. The effect of a monoclonal antibody to tumor necrosis factor on survival from childhood cerebral malaria. *J Infect Dis* 1996;**174**:1091–7.
43 Nussler AK, Eling W, Kremsner PG. Patients with Plasmodium falciparum malaria and Plasmodium vivax malaria show increased nitrate and nitrate plasma levels. *J Infect Dis* 1994;**169**:1418–19.
44 Al Yaman FM, Mokela D, Genton B, *et al*. Association between serum levels of reactive nitrogen intermediates and coma in children with cerebral malaria in Papua New Guinea. *Trans R Soc Trop Med Hyg* 1996;**90**:270–3.
45 al-Yaman FM, Genton B, Clark IA. The ratio of reactive nitrogen intermediates to tumour necrosis factor and clinical outcome of falciparum malaria disease. *Trans R Soc Trop Med Hyg* 1998;**92**:417–20.
46 Anstey NM, Weinberg JB, Wang Z, *et al*. Effects of age and parasitemia on nitric oxide production/leukocyte nitric oxide synthase type 2 expression in asymptomatic, malaria-exposed children. *Am J Trop Med Hyg* 1999;**61**:253–8.
47 Agbenyega T, Angus B, Bedu-Addo G, *et al*. Plasma nitrogen oxides and blood lactate concentration in Ghanaian children with malaria. *Trans R Soc Trop Med Hyg* 1997; **91**:298–302.
48 Weiss G, Thuma PE, Biemba G, *et al*. Cerebrospinal fluid levels of biopterin, nitric oxide metabolites, and immune activation markers and the clinical course of human cerebral malaria. *J Infect Dis* 1998;**177**:1064–8.
49 Dobbie MS, Crawley J, Waruiru C, *et al*. CSF studies in children with cerebral malaria: an excitoxic mechanism? *Am J Trop Med Hyg* 2000;(in press).
50 Taylor AM, Day NPJ, Sinh DXT, *et al*. Reactive nitrogen intermediates and outcome in severe adult malaria. *Trans R Soc Trop Med Hyg* 1998;**92**:170–5.
51 Warrell DA, Looareesuwan S, Warrell MJ, *et al*. Dexamethasone proves deleterious in cerebral malaria. A double-blind trial in 100 comatose patients. *N Engl J Med* 1982;**306**: 313–19.
52 Warrell DA, Molyneux ME, Beales PF. Severe and complicated malaria. *Trans R Soc Trop Med Hyg* 1990;**84**(suppl 2):1–65.
53 Molyneux ME, Taylor TE, Wirima JJ, *et al*. Clinical features and prognostic indicators in paediatric cerebral malaria: a study of 131 comatose Malawian children. *Q J Med* 1989; **71**:441–59.
54 White NJ, Looareesuwan S. Cerebral malaria. In: Kennedy PGE, Johnson RI, eds. *Infections of the nervous system*. London: Butterworths, 1987:118–43.
55 White NJ, Warrell DA, Chanthavanich P, *et al*. Severe hypoglycemia and hyperinsulinemia in falciparum malaria. *N Engl J Med* 1983;**309**:61–6.
56 Taylor TE, Molyneux ME, Wirima JJ, *et al*. Blood glucose levels in Malawian children before and during the adminstration of intravenous quinine for severe falciparum malaria. *N Engl J Med* 1988;**319**:1040–7.
57 Looareesuwan S, Warrell DA, White NJ, *et al*. Retinal hemorrhage, a common sign of prognostic significance in cerebral malaria. *Am J Trop Med Hyg* 1983;**32**:911–15.
58 Lewallen S, Harding SP, Ajewole J, *et al*. A review of the spectrum of clinical ocular fundus findings in P falciparum malaria in African children with a proposed classification and grading system. *Trans R Soc Trop Med Hyg* 1999;**93**: 619–22.
59 White NJ, Looareesuwan S, Phillips RE, *et al*. Single dose phenobarbitone prevents convulsions in cerebral malaria. *Lancet* 1988;ii:64–6.
60 Marsh K, Forster D, Waruiru C, *et al*. Indicators of life-threatening malaria in African children. *N Engl J Med* 1995;**332**:1399–404.
61 Waruiru cerebral malaria, Newton CR, Forster D, *et al*. Epileptic seizures and malaria in Kenyan children. *Trans R Soc Trop Med Hyg* 1996;**90**:152–5.
62 Gordeuk V, Thuma P, Brittenham G, *et al*. Effect of iron chelation therapy on recovery from deep coma in children with cerebral malaria. *N Engl J Med* 1992;**327**:1473–7.
63 Newton CRJC, Chokwe T, Schellenberg JA, *et al*. Coma scales for children with severe falciparum malaria. *Trans R Soc Trop Med Hyg* 1997;**91**:161–5.
64 Bondi FS. The incidence and outcome of neurological abnormalities in childhood cerebral malaria: a long term

follow up of 62 surviviors. *Trans R Soc Trop Med Hyg* 1992; **86**:17–19.
65 Crawley J, Smith S, Kirkham FJ, *et al*. Seizures and status epileticus in childhood cerebral malaria. *Q J Med* 1996;**89**: 591–7.
66 Crawley J, English M, Waruiru C, *et al*. Abnormal respiratory patterns in childhood cerebral malaria. *Trans R Soc Trop Med Hyg* 1998;**92**:305–8.
67 Brewster DR, Kwiatkowski D, White NJ. Neurological sequelae of cerebral malaria in children. *Lancet* 1990;**336**: 1039–43.
68 Walker O, Salako LA, Sowunmi A, *et al*. Prognostic risk factors and post mortem findings in cerebral malaria in children. *Trans R Soc Trop Med Hyg* 1992;**86**:491–3.
69 Waller D, Krishna S, Crawley J, *et al*. Clinical features and outcome of severe malaria in Gambian children. *Clin Infect Dis* 1995;**21**:577–87.
70 Newton CR, Kirkham FJ, Winstanley PA, *et al*. Intracranial pressure in African children with cerebral malaria. *Lancet* 1991;**337**:573–6.
71 Waller D, Crawley J, Nosten F, *et al*. Intracranial pressure in childhood cerebral malaria. *Trans R Soc Trop Med Hyg* 1991;**85**:362–4.
72 Newton CR, Peshu N, Kendall B, *et al*. Brain swelling and ischaemia in Kenyans with cerebral malaria. *Arch Dis Child* 1994;**70**:281–7.
73 Newton CRJC, Marsh K, Peshu N, *et al*. Perturbations of cerebral hemodynamics in Kenyan children with cerebral malaria. *Pediatr Neurol* 1996;**15**:41–9.
74 Newton CR, Crawley J, Sowumni A, *et al*. Intracranial hypertension in Africans with cerebral malaria. *Arch Dis Child* 1997;**76**:219–26.
75 Clavier N, Rahimy C, Ayivi B, *et al*. No evidence for cerebral hypoperfusion during cerebral malaria. *Crit Care Med* 1999;628–32.
76 Holding PA, Stevenson J, Peshu N, *et al*. Cognitive sequelae of severe malaria with impaired consciousness. *Trans R Soc Trop Med Hyg* 1999;**93**:529–34.
77 Collomb H, Rey M, Dumas M, *et al*. Les hemiplegies au cours du paludisme aigu. *Bulletin de la Societe D'Afrique Noire de longue Francaise* 1967;**7**:791–5.
78 Omanga U, Ntihinyurwa M, Shako D, *et al*. Les hemiplegies au cours de l'acces pernicieux a plasmodium falciparum de l'enfant. *Annals de Pediatrie* 1983;**30**:294–6.
79 Wattanagoon Y, Srivilairit S, Looareesuwan S, *et al*. Convulsions in childhood malaria. *Trans R Soc Trop Med Hyg* 1994;**88**:426–8.
80 Luijckx GJ, De Krom MC, Takx-Kohlen BC. Does chloroquine cause seizures? Presentation of three new cases and a review of the literature. *Seizure* 1992;**1**:183–5.
81 English M, Waruiru C, Marsh K. Transfusion for respiratory distress in life-threatening childhood malaria. *Am J Trop Med Hyg* 1996;**55**:525–30.
82 Looareesuwan S, Wilairatana P, Krishna S, *et al*. Magnetic resonance imaging of the brain in patients with cerebral malaria. *Clin Infect Dis* 1995;**21**:300–9.
83 van der Torn M, Thuma PE, Mabeza GF, *et al*. Loading dose of quinine in African children with cerebral malaria. *Trans R Soc Trop Med Hyg* 1998;**92**:325–31.
84 White NJ, Looareesuwan S, Warrell DA, *et al*. Quinine pharmacokinetics and toxicity in cerebral and uncomplicated Falciparum malaria. *Am J Med* 1982;**73**:564–72.
85 Hien TT, White NJ. Qinghaosu. *Lancet* 1993;**341**:603–8.
86 White NJ. The treatment of malaria. *N Engl J Med* 1996;**335**:800–6.
87 van Hensbroek MB, Onyiorah E, Jaffar S, *et al*. A trial of artemether or quinine in children with cerebral malaria. *N Engl J Med* 1996;**335**:69–75.
88 Hien TT, Day NP, Nguyen HP, *et al*. A controlled trial of artemether or quinine in Vietnamese adults with severe falciparum malaria. *N Engl J Med* 1996;**335**:76–83.
89 McIntosh HM, Olliaro P. Treatment of severe malaria with artemisinin derivatives. A systematic review of randomised controlled trials. *Med Trop (Mars)* 1998;**58**:61–2.
90 Hien TT, Arnold K, Vinh H, *et al*. Comparison of artemisinin suppositories with intravenous artesunate and intravenous quinine in the treatment of cerebral malaria. *Trans R Soc Trop Med Hyg* 1992;**86**:582–3.
91 Winstanley PA, Newton CR, Pasvol G, *et al*. Prophylactic phenobarbitone in young children with severe falciparum malaria: pharmacokinetics and clinical effects. *Br J Clin Pharmacol* 1992;**33**:149–54.
92 Crawley J, Waruiru C, Mithwani S, *et al*. Phenobarbitone halves the seizure frquency, but doubles the mortality in childhood cerebral malaria: results of a double blind, randomised controlled trial. *Lancet* 2000;**26**:355:701–6.
93 Hoffman SL, Rustama D, Punjabi NH, *et al*. High-dose dexamethasone in quinine-treated patients with cerebral malaria: a double-blind, placebo-controlled trial. *J Infect Dis* 1988;**158**:325–31.
94 Looareesuwan S, Phillips RE, Karbwang J, *et al*. Plasmodium falciparum hyperparasitaemia: use of exchange transfusion in seven patients and a review of the literature. *Q J Med* 1990;**227**:471–81.
95 Miller KD, Greenberg AE, Campbell CC. Treatment of severe malaria in the United States with continous infusions of quinidine gluconate and exchange transfusion. *N Engl J Med* 1989;**321**:65–70.
96 White NJ. Lumbar puncture in cerebral malaria. *Lancet* 1991;**338**:640–1.
97 Winstanley PA, Mberu EK, Watkins WM, *et al*. Towards optimal regimens of parenteral quinine for young African children with cerebral malaria: unbound quinine concentrations following a simple loading dose regimen. *Trans R Soc Trop Med Hyg* 1994;**88**:577–80.
98 McCaslin RI, Pikis A, Rodriquez WJ. Pediatric Plasmodium falciparum malaria: a ten-year experience from Washington DC. *Pediatr Infect Dis J* 1994;**13**:709–15.
99 Thuma PE, Mabeza GF, Biemba G, *et al*. Effect of iron chelation therapy on mortality in zambian children with cerebral malaria. *Trans R Soc Trop Med Hyg* 1998;**92**:214–18.
100 Di Perri G, Di Perri IG, Monteiro GB, *et al*. Pentoxifylline as a supportive agent in the treatment of cerebral malaria in children. *J Infect Dis* 1995;**171**:1317–22.
101 Davis TM, Supanaranond W, Pukrittayakamee S, *et al*. A safe and effective consecutive-infusion regimen for rapid quinine loading in severe falciparum malaria. *J Infect Dis* 1990;**161**:1305–8.
102 White NJ, Looareesuwan S, Warrell DA, *et al*. Quinine loading dose in cerebral malaria. *Am J Trop Med Hyg* 1983; **32**:1–5.
103 Phillips RE, Warrell DA, White NJ, *et al*. Intravenous quinidine for the treatment of severe falciparum malaria. Clinical and pharmacokinetic studies. *N Engl J Med* 1985; **312**:1273–8.
104 Murphy SA, Mberu E, Muhia D, *et al*. The disposition of intramuscular artemether in children with cerebral malaria; a preliminary study. *Trans R Soc Trop Med Hyg* 1997;**91**: 331–4.